

Research Article

Design, Development and Evaluation of Press Coated Tablets of an Antihypertensive Drug

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Abstract: In the present study, an attempt was made to design and evaluate a press coated tablet of Losartan Potassium, in Order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. The tablets, each consisting of a core and a coat, were prepared using compression coating technique. The coat layer consists of HPMC K100M and Ethyl cellulose in different ratio. The tablets were evaluated for different parameters like weight variation, friability, in-vitro release, content uniformity, Hardness. Observations of all the formulations for physical characterization had shown that, all of them comply with the official compendia's. Results of *in-vitro* drug release profile from all formulations (F1-F4) showed slow and sustained release of Losartan potassium over a period of 12 hours. Hydrophilic polymer like, HPMC K100M (60%) and Ethyl cellulose (10%) was found to be optimum. HPMC K100M was useful in the formation of matrix and Ethyl cellulose was used as its swellable and rupturable behavior. DSC and IR studies show no evidence on interaction between drug, polymers and other excipients. The best fit model for the optimized batch was peppas having *r* value 0.9938, *n* value 0.6998 and *K* value is 19.5516.

Keywords: Press coated Tablet, Losartan Potassium, Ethyl cellulose, core tablet.

INTRODUCTION

An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems greater attention has been focused on sustained release drug delivery system [1, 2]. Press-coated formulation can be used to protect hygroscopic, light-sensitive, oxygenable or acid-labile drugs, to separate incompatible drugs from each other or to achieve sustained release. Intermittent release can also be achieved by incorporating one portion of drug in the core and the other in the coat. Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating progress and use of coating solutions. Material such as hydrophilic cellulose derivates can be used. Most such formulations release drug after a lag phase, followed by a rapid dissolution of a core. A press-coated device in which the inner core contains the drug and the outer coat is made of different types of polymers [3, 4]. The outer barrier, controlling drug release can be either swellable or erodible. Lag times can be varied by

changing the barrier formulation or the coating thickness [5].

Losartan potassium is a potent, highly specific angiotensin II type 1(AT 1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastro intestinal tract with oral bioavailability of about 33% and a plasma half-life ranging from 1.5 to 2.5 hour [6]. The objective of the present study was to formulate and evaluate press coated tablets, from which the drug is released in a controlled manner through a specialized coated oral sustained drug delivery system by using hydrophilic polymer .HPMC K100M and Ethyl cellulose.

MATERIALS AND METHODS

Losartan potassium was obtained as kind gift sample by Wockhardt Pharma.Ltd, Aurangabad (Maharashtra) India. Ethyl cellulose & HPMC K100M was obtained as gift sample by Purechem Lab, Mumbai. All other materials and solvents used were of analytical grade.

Differential Scanning Calorimetry study

Thermographs of pure drug, polymers and their physical mixers were recorded. An empty aluminium pan was used as reference [7, 8]. DSC measurement

was performed at a heating rate of $10^0\text{C}/\text{min}$ from 40^0 to 300^0C using aluminium sealed pan. During the measurement, the sample size was 1-4 mg for each measurement and sample cell was purged with nitrogen gas.

Infrared spectra analysis

IR spectroscopy was also used to determine the molecular interaction between polymer and drug. All physical mixtures and drug sample were mixed with dried KBR in ratio 1.100. Then small fraction of mixture was compressed on automatic IR press (Kimaya Engg. Thane, India) at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellet was taken on FTIR spectrophotometer (Shimadzu, 8400S, Kyoto, Japan) [9, 10].

Preparation of core tablet

The inner core tablets were prepared by using direct compression method. Powder mixture of losartan potassium, sodium starch glycolate, microcrystalline cellulose and lactose ingredients were dry blended for 20 mins. Followed by addition of magnesium stearate. The mixture was then further blended for 10 mins; 100 mg of resultant powder blend was manually compressed with 6 mm punch and die to obtain the core tablet (A Jaguar JMD-4-9 Ltd, Mumbai).

Table 1: Composition of Core Tablet

Sl. No.	Ingredients	Amount(mg)
1	Losartan Potassium	50
2	Sodium Starch Glycolate	2
3	MCC	30
4	Lactose	2
5	Mg. Stearate	16

Preparation of press-coated tablet

The coat layer of 150 mg obtained from different polymeric mixtures of different ratios was divided in to two fractions, each 75 mg to act as upper and lower coat. The press coating of tablets was performed using a rotary tablet machine. A half amount of the powder (lower coat) was filled into the die to make a powder bed, in the center of which core tablet was placed manually. Then, the remaining half of the coating material filled in the die (upper coat), and the contents were compressed under a sufficient compression force, using a flat punch 8 mm in diameter. Given in table no.2

Table 2: Composition of press coated tablet

Formulation Code	Drug (mg)	Core tablet (mg)	Ethyl Cellulose (mg)	HPMC K 100M (mg)
F1	50	100	7.5	142.5
F2	50	100	15	135
F3	50	100	22.5	127.5
F4	50	100	30	120

*Each formulation contains 50 mg of Losartan potassium and the total weight of core tablet is 70 mg.

Evaluation of precompression parameter of powder blend

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated [11-14].

Evaluation of Press-Coated Tablet

Tablets from all the formulations were evaluated for various properties like hardness, Friability and weight variation.

1. Uniformity of drug content

2. Six tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 50 mg of Losartan potassium was weighed and dissolved in 100 ml of 0.1 N HCl. From this solution, 1ml sample was withdrawn and diluted to 10 ml with 0.1 N HCl. The absorbance was measured at wavelength 234 nm using double beam UV-Visible spectrophotometer [15].

Content uniformity was calculated using formula

$$\% \text{ Purity} = 10 C (Au / As)$$

Where, C: Concentration, Au and As: Absorbance's obtained from standard preparation and assay preparation respectively.

In-vitro dissolution studies

In-vitro release study of Losartan potassium press-coated tablet was carried out (USP dissolution test apparatus Type-II Paddle type) using 900 ml of 0.1 N HCl (pH 1.2) solutions for two hours and later on phosphate buffer (pH 6.8) for further ten hours as a dissolution medium. The paddles were rotated at 100 rpm. The medium was set at $37 \pm 0.5^0\text{C}$. Aliquot (10 ml) of the solution was collected from the dissolution apparatus hourly and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV spectrophotometer at 234 nm using 0.1N HCl or pH 6.8 buffer as a blank. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Drug content in dissolution sample was determined by software (PCP disso v2.08) version [16].

Kinetics of *In-vitro* Drug Release

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order,

Higuchi matrix, Peppas and Hixson Crowell model using PCP-DISSO – v2 software [17, 18].

Accelerated stability study

Accelerated stability study of formulation was carried out as per ICH Guideline to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions.¹⁹ Chemical and physical stability of microsphere formulation was assessed at 40 ± 2 °C and 75 ± 5 % RH as per ICH Guidelines. Microsphere was filled in sealed vial with aluminium foil and stored for 180 days in stability chamber (CIS-24 REMI Instruments Ltd, India). Samples were analyzed for drug content and % cumulative release during time period of 3 months.

RESULTS AND DISCUSSION

FTIR Spectroscopy

IR spectra for Losartan potassium, HPMC K100M, Ethyl cellulose and physical mixture of Losartan

potassium are given in fig.1-4. Major functional groups of Losartan potassium (C-H stretching of benzene ring) at 1502 and 1538, (C-H Stretching of alkane) at 2902 C-H bending of alkane) at 2902, (C=C Stretching of alkene) at 1602, Di-Substituted Ar-ring) at 800 (C=N stretching) at 2898 (C-N vibrations) at 1195, (C=O stretching) at 1723 can be seen in spectra of individual drugs as well as in spectra of physical mixture. So there is no interaction between Losartan potassium HPMC K100M, Ethyl cellulose the results of the above study show that various peaks which were observed in official spectra of Losartan potassium matches with obtained spectra of Losartan potassium which confirms about the identity and purity of drug.

The FT-IR spectra of Losartan potassium, HPMC K100M, Ethyl cellulose and mixture of drug-polymer were recorded and No any peak observed in IR spectra indicating no chemical interaction between drug and polymers.

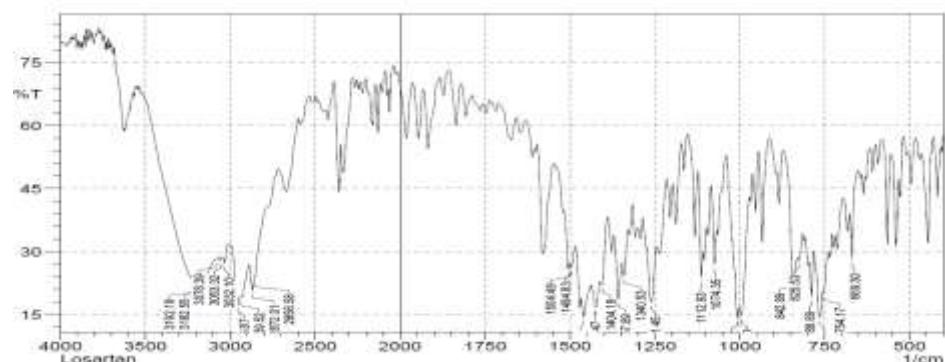


Fig. 1: FTIR spectrum of Losartan potassium

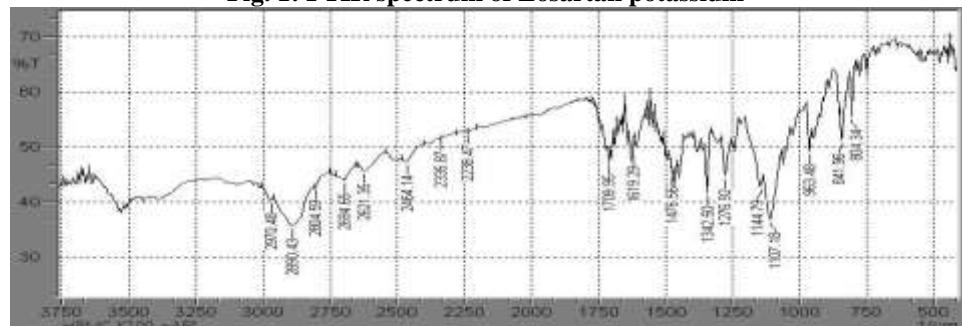


Fig. 2: FTIR spectrum of Losartan potassium + HPMC K100M

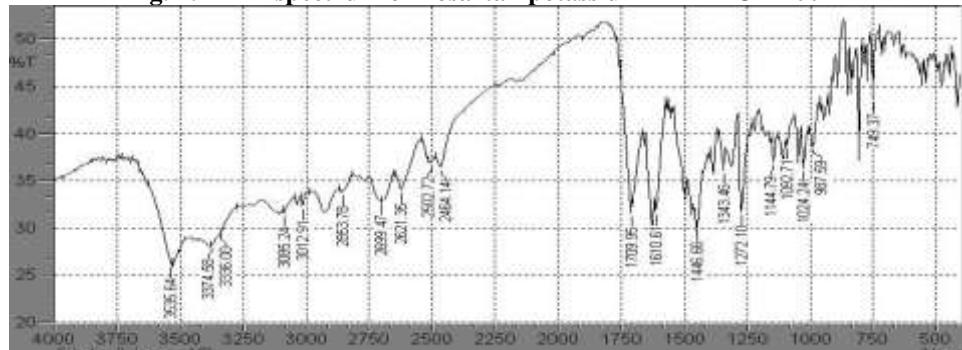


Fig. 3: FTIR spectrum of Losartan potassium + Ethyl cellulose

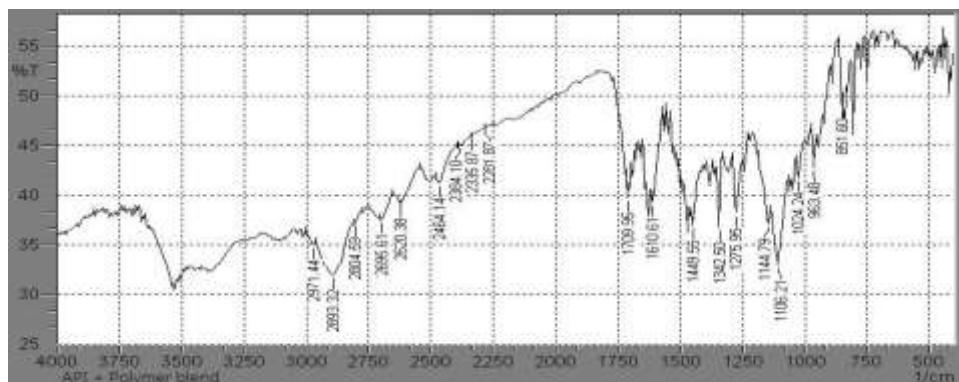


Fig. 4: FTIR spectrum of Physical mixture

Differential Scanning Calorimetry (DSC)

DSC thermograms showed that there was no any major difference in onset temperature and peak

temperature, when compared with pure drug's thermograms Fig. 5 & 6. No interaction was found between drug and polymers. Results are shown as

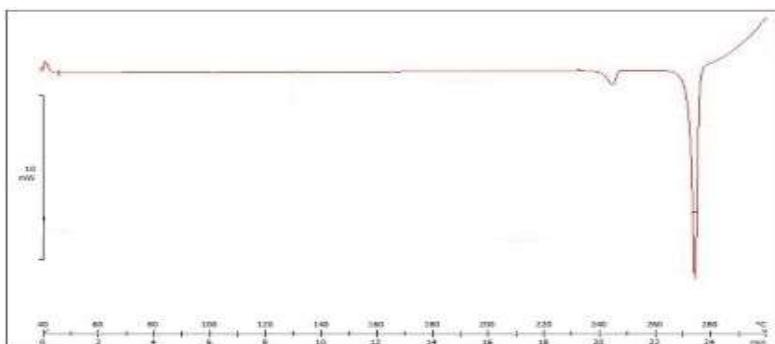


Fig. 5: DSC Thermogram of Losartan potassium

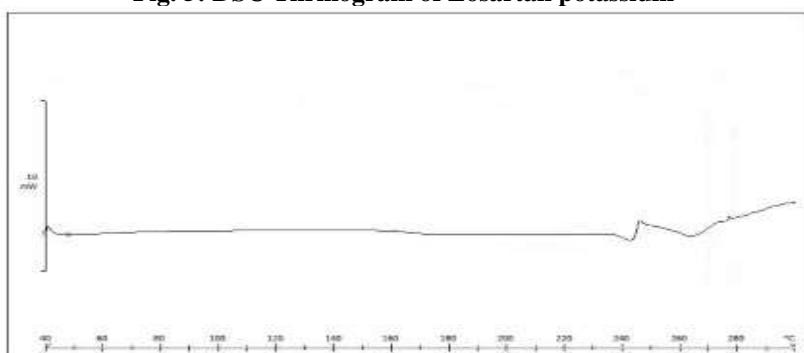


Fig. 6: DSC Thermogram of Physical mixture

Physical Evaluation of granules

Physical evaluation of granules showed good physical property the bulk density of granules was found to be between 0.22 ± 0.01 to 0.25 ± 0.02 g/cm. This indicates good packing capacity of granules. Carr's index was found to be between 16.7 ± 0.6 to 19.5 ± 0.4

showing good flow characteristics. Hausner ratio low range was indicates good flow ability. The angle of repose of all the formulations within the range of 23.6 ± 0.7 to 26.5 ± 0.4 i.e. granules were of good flow properties.

Table 3: Micromeritic properties of Losartan potassium press coated tablets (n=3)

Batch	Bulk density (g/ml) (mean \pm SD)	Tapped density (g/ml) (mean \pm SD)	Compressibility index (%) (mean \pm SD)	Angle of repose(θ) (mean \pm SD)	Hausner's ratio (%)
F1	0.22 ± 0.01	0.32 ± 0.04	16.7 ± 0.6	26.5 ± 0.4	1.16 ± 0.01
F2	0.23 ± 0.03	0.29 ± 0.02	17.6 ± 0.7	23.6 ± 0.7	1.14 ± 0.02
F3	0.22 ± 0.01	0.28 ± 0.02	19.5 ± 0.4	25.5 ± 0.4	1.12 ± 0.03
F4	0.25 ± 0.02	0.30 ± 0.03	18.4 ± 0.6	24.6 ± 0.6	1.10 ± 0.01

The hardness of tablet was in range of 2.5 ± 0.33 to 4.8 ± 0.38 measured by Monsanto hardness tester. The friability was in range of 0.451 ± 0.09 to

0.87 ± 0.12 . The values of average weight are within limit.

Table 4: Physical evaluation of Losartan potassium press coated tablet

Formulation	Thickness [#]	Hardness (kg/cm ²) \pm SD [*]	Friability (%)	Weight Variation (mg) \pm SD [#]
Core tablet	1.15 ± 0.02	2.5 ± 0.33	0.87 ± 0.12	0.90 ± 15
F1	3.9 ± 0.06	4.8 ± 0.38	0.719 ± 0.10	197.79 ± 1.24
F2	3.45 ± 0.05	4.7 ± 0.32	0.687 ± 0.14	203.05 ± 1.29
F3	3.39 ± 0.05	4.6 ± 0.26	0.517 ± 0.11	198.86 ± 1.02
F4	3.63 ± 0.04	4.82 ± 0.28	0.451 ± 0.09	199.16 ± 1.12

^{*}(n=3)

From all the formulations F1 to F4 first batch F1 was shown maximum (97.70%) drug release at 5 hr, so its fail to carry out the drug at pH 6.8 buffer solution. After then batch F2,F3 and F4 shows better results, and

among those batch F2 shows maximum % drug release(1:2:18) i.e. 99.49% within a 10 hrs, so it was selected as optimum formulation.

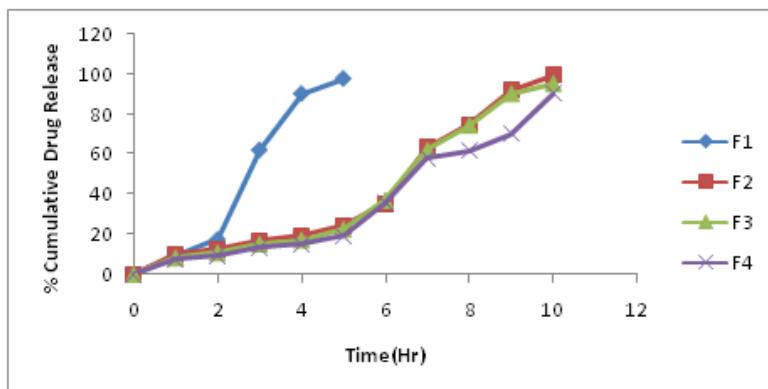


Fig. 7: % Cumulative drug release of F1 to F4

The *in vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism shown in table no. 22. The best fit model

for the optimized batch F2 is peppas having r value 0.9938, n value 0.6998 and K value is 19.5516.

Table 5: Kinetic data for the prepared batches

Formulations	Best Fit Model	r ²	K	n (Peppas)
F1	Matrix	0.9645	25.7704	0.5879
F2	Peppas	0.9938	19.5516	0.6998
F3	Peppas	0.9872	17.3370	0.7360
F4	Peppas	0.9895	19.7269	0.6729

Accelerated stability studies (AST) was carried for optimized batch F2 by exposing it to environmental condition like $40^{\circ}\text{C}/75\%$ RH for one month. The sample was taken at different time interval 45, 90, 135,

and 180 day and analyzed for physical parameters like hardness, uniformity of content and percentage cumulative drug release.

Table 6: Accelerated stability study of F2 formulation

Sr. no.	Days	Colour	Drug content (%)	Cumulative release (%)
			Mean \pm SD (n=3)	
1	0	No change	96.5 \pm 0.70	99.90 \pm 0.45
2	45	No change	95.73 \pm 0.20	99.85 \pm 0.97
3	90	No change	95.08 \pm 0.16	98.76 \pm 0.32
4	135	No change	94.96 \pm 0.9	97.47 \pm 0.78
5	180	No change	94.96 \pm 0.12	97.58 \pm 0.16

CONCLUSION

Losartan potassium was selected for this investigation because less biological half life, to improve bioavailability by retaining the drug in acidic environment as its solubility decreases with increasing pH and to reduce wastage. Step by step studies were carried out to develop and evaluate oral sustain release tablet for Losartan potassium using hydrophilic polymers. The oral sustain release tablets were prepared by direct compression press coating technique using rate controlling hydrophilic polymers. In the preliminary trials, the effect of various polymers i.e. HPMC K100M, and Ethyl cellulose was studied on their different ratios to produce time release tablet of losartan potassium. HPMC K100M, Ethyl cellulose was found to be suitable for press coating. Physical parameters like hardness, weight variation, thickness and friability were within pharmacopoeial limit. Percentage drug content in all press coated tablet formulations was found to be 70.26% to 78.28% which was within pharmacopoeial limit. The best fit model for the optimized batch F2 is peppas having r value 0.9938, n value 0.6998 and K value is 19.5516.

REFERENCES

- Chien YW; Novel Drug delivery Systems. Marcel Dekker, Inc., New York, U.S.A., 1992: 139-196.
- Brahmankar DM, Jaiswal BS; Controlled release medication. In Brahmankar DM, Jaiswal BS editors; Text book of biopharmaceutics and pharmacokinetics a treatise, 1st edition. Delhi, Vallabh Prakashan, 1995: 335-340.
- Jain KK; Drug delivery systems – An overview. In Jain KK editor; Drug delivery systems. New Jersey, Humana Press, 2008: 1-50.
- Janugade BU, Patil SS, Patil SS, Lade PD; Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system. Int J Chem Tech Res., 2009; 1(3): 690-695.
- Fukui E, Uemura K., Kobayashi M; Studies on applicability of press coated tablet using hydroxypropylcellulose (HPC) in the outer shell for timed release preparation. Int J Control Release, 2000; 68(2): 215-223.
- Goldsmith JA, Randall N, Ross SD; On methods of expressing dissolution rate data. J Pharm Pharmacol., 1978; 30(1): 347-349.
- Schimdt P; Secondary electron microscopy in pharmaceutical technology. In Swarbrick J, Boylon JC editors; Encyclopedia of Pharmaceutical Technology. 3rd edition, volume 5, Marcel Dekker Inc., New York, 2007: 3217- 325.
- Duerst M; Spectroscopic methods of analysis: Infrared Spectroscopy. In Swarbrick J, Boylon JC editors; Encyclopedia of Pharmaceutical Technology. 3rd edition, volume 5, Marcel Dekker Inc. New York, 2007: 3405- 3418.
- Qin W, Zhang GGZ; Stability and excipient compatibility study. Novartis, 2006: 30-35.
- Stuart B; Infrared spectroscopy - Fundamental and application. John Wiley and sons, 2004: 46-63.
- Sinko PJ; Martin's physical pharmacy and pharmaceutical sciences. 5th edition, Noida, BI Publisher, 2006: 550-560.
- Martin A, Swarbrick G, Physical Pharmacy, Physical Chemical Principal of Pharmaceutical Science. 3rd editor, Varghese publication house, 1991: 518-519.
- Aulton ME; Pharmaceutics: The science of dosage form design. 2nd edition, Churchill Livingstone, New York, 2002: 290-291.
- Banker SG, Anderson RN; Tablets. In Lachman L, Liberman AH, Kanig LJ editors; Text Book of the Theory and Practice of Industrial Pharmacy. 3rd editors, Mumbai, Varghese Publication House, 1991:317-324.
- British Pharmacopoeia; British Pharmacopoeial Commission, London: Stationery Office Books, 2004; 2: 1745-46.
- USP 32 NF 27, the United States Pharmacopoeial Commission, Rockville, MD, 2009; 2: 1811-1820.
- Higuchi T; Mechanism of sustained action medicament, Theoretical analysis of rate release of solid drugs dispersed in solid matrices, J Pharm Sci., 1963; 52(12):1145- 1149.
- Korsmeyer RW, Gunny R, Peppas NA; Mechanism of solute release from porous hydrophilic polymers. Int J Pharmaceutics, 1983;15(1): 25-35.
- Methews BR; Regulatory aspects of stability testing in Europe. Drug Dev Ind Pharm., 1999; 25(7): 831-856.